II. REMARKS

Before the amendments made herein, claims 71, 72, 92-101, 107-111, and 114-118 were pending. Claims 71, 72, 92-96, 107-111, and 114-118 have been canceled herein without prejudice. In addition, claims 119-127 have been added herein. Accordingly, after the amendments made herein are entered, claims 97-101, and 119-127 will be pending.

A. Regarding the amendments

New claims 119-122 are directed to the preparation of claim 97 that includes a polypeptide that is at least 96-99% homologous to SEQ ID NO:10. The claims are supported in the specification, for example, at page 59, line 5.

New claims 123 and 124 are directed to heparanase that comprises amino acid residues 12 to 136 of SEQ ID NO:10. The claims are supported in the specification, for example, at page 104, lines 5-6, which discloses this portion of human heparanase (i.e., SEQ ID NO:10).

New claims 125, and 126 are directed to heparanase that comprises amino acid residues 500 to 543 of SEQ ID NO:10. The claims are supported in the specification, for example, at page 104, lines 7-8, which discloses this portion of human heparanase (i.e., SEQ ID NO:10).

Finally, new claim 127 is to the variant of SEQ ID NO:10, which is disclosed in the specification, for example, in Figure 1 and at page 44, lines 14-20.

Because all of the amendments made herein are fully supported by the specification, no issue of new matter arises.

B. Regarding the claim objections

The claims are objected to for reciting the term "including." The Action suggests replacing this term with the term "comprises" to be more in alignment with the standard that is used in the art.

To promote prosecution of the subject application, Applicants have so amended herein. Accordingly, removal of this objection is respectfully requested.

C. Regarding the enablement rejection

All of the claims pending in the last and current response, except for claim 101, are rejected under 35 U.S.C. §112, first paragraph, as allegedly non-enabling. Applicants respectfully traverse the rejection.

The Examiner's main point in the current Action is that the guidance provided is not sufficient for the skilled artisan to determine "which of the **infinite** number of variants have [heparanase] activity." To underscore this point, the Action alleges that, with 80% amino acid identity to SEQ ID NO:10 (which has 543 residues) would mean that 2.1×10^{-18}% of random mutants would be active.

In response to this line of argument, Applicants respectfully submit herewith a copy of the decision of the Board of Patent Appeals and Interferences in *Ex Parte Sun*. The claim in question in *Sun* relates to a polynucleotide (which obviously is quite long) having at least 80% identity to the entire coding region of SEQ ID NO:1 (which encodes a "WEE1 protein"). The claim was rejected as allegedly not enables by the specification. On page 11 of the decision, the Board summarizes the examiner's position, which is very similar to the position taken by the Examiner in this case. In fact, the Examiner can surely appreciate how very few sequences (perhaps fewer than 2.1×10^{-18}%!) would likely encode an active WEE1 protein.

On page 14 of the decision, the Board rejected the examiner's position. First, the Board pointed out that the chemical structure of the claimed sequence is disclosed. Similarly, the chemical structure of SEQ ID NO:10 is disclosed in the subject specification.

Second, the Board noted that the specification provides an example for how to screen for WEE1 activity. Similarly, the subject specification discloses how to screen for heparanase activity. See, for example, Figures 9a and b and page 47, lines 14-21, which show testing for such activity by measuring the level of peak II HS degradation fragments. See also the Examples section.

Finally, the Board found that the specification in *Sun* gives very general guidance about where to vary the protein. Specifically, "most of the variations in the amino acid sequences of WEE1 are in the amino terminus, while the carboxy end of the genes are relatively conserved."

Similarly, as introduce in the previous response, an analysis of the alignment data shown in Figure 17 of the subject specification provides ample guidance to the skilled artisan on how to make active heparanase variants. For example, residues 85-106 are identical among the variants shown in Figure 17. By contrast, for example, residues 23-36 have 11 residue differences.

Furthermore, comparing rat and human, residues 129-138, for example, have 8 differences among the 10 residues, with 9 of 10 differences among mouse and human at this region. With such guidance, the skilled artisan would know to not vary residues 85-106 and to vary one or more residues among residues 23-36 and/or 129-138, especially with a similar substitution (e.g., hydrophilic) as discussed above. The skilled

artisan could even further use the guidance of the subject specification to replace one or more amino acid residues in SEQ ID NO:10, especially in these highly variable regions, with those corresponding residues found in mouse or rat heparanase.

Looking at the protein more broadly, residues 49-109 make up 61 residues. Comparing mouse and human region at this region, there are only 10 of 61 changes. Comparing rat and human at this region, there are also only 10 of 61 changes. This is a remarkably conserved region, one that the skilled artisan would likely not vary, at least as a starting point, in trying to obtain additional heparanase homologs.

Indeed, as it turns out, the conserved region of residues 49-109 was confirmed to be the 8 kDa unit of active heparanase. By contrast, variable regions 23-36 and 129-138, discussed above, are not part of either the small or large units of mature heparanase.

Applicants respectfully submit that this alignment data is far more information that the guidance cited in *Sun*. For in *Sun*, there is no mention of any other WEE1 gene or protein. By contrast, Applicant has provided several other heparanases, with as little as 65% homology to SEQ ID NO:1. Given the facts and rationale by the Board in the *Sun* case, Applicants respectfully request that this rejection be withdrawn.

D. Regarding the anticipation rejection

All of the claims pending in the last response continue to be rejected under 35 U.S.C. §102 as allegedly anticipated by Fuks et al. (U.S. Pat. No. 5,362,641; hereinafter "Fuks"). Applicants respectfully traverse the rejection, noting that many of the claims under this rejection have been canceled herein without prejudice, while several new claims have been added herein.

To promote prosecution of the subject application, Applicants have cancelled herein several claim sets. The remaining claims, as currently pending, now all require that the recited preparation of heparanase be able to elicit anti-heparanase antibodies.

The current Action acknowledges (and concedes) to what Applicants have already declared – namely, that the preparation taught by Fuks could not elicit anti-heparanase antibodies. Rather, this preparation elicited anti-PAI-1 antibodies.

Given the Action's acknowledgment, Applicants are at a complete loss as to why the subject claims requiring that the preparation of heparanase be able to elicit anti-heparanase antibodies continue to be rejected as anticipated by Fuks. The Action provides no rationale or reasoning for this continued rejection.

What if Applicants' claims were to 90% purity and Applicants provided ample evidence that, despite all efforts, Fuks could only get its preparation to 80% purity – would the Action then argue that Fuks somehow had the "potential" to be 90% pure? The circumstances here are no different.

Simply put, all of the pending claims require that the recited preparation of heparanase be able to elicit anti-heparanase antibodies. As the Action concedes and despite efforts to do so, the preparation taught by Fuks could not elicit anti-heparanase antibodies. Accordingly, Applicants respectfully request that this rejection be withdrawn.

III. CONCLUSION

All of the issues raised in the Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

Martin D. Moynihan
Registration Number 40,338

Date: February 1, 2006

Encl:

1. Request for One Month Extension Fee; and
2. Ex parte Sun Reference